

WHY IS LOW BLOOD CHOLESTEROL ASSOCIATED WITH RISK OF NONATHEROSCLEROTIC DISEASE DEATH?

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KEY WORDS: coronary heart disease, cancer

INTRODUCTION

There is strong and congruent evidence that serum cholesterol and its lipoprotein components play a critical role in the development of coronary heart disease (CHD) through a causal role in atherogenesis. Recent evidence shows that reduction of serum total cholesterol (TC), particularly the low-density lipoprotein (LDL) cholesterol fraction, reduces the incidence of CHD (1-14), by arresting or reversing the progression of atherosclerosis (15-17). Methodologically and historically, two studies were weighted particularly heavily in development of US TC-lowering policies. The Lipid Research Clinics Coronary Primary Prevention Trial found a 19% reduction in CHD incidence, by reducing TC with a combination of diet plus cholestyramine, compared with TC lowering with diet alone (5). The Helsinki study of TC lowering, which used gemfibrozil compared with placebo, found a 34% reduction in CHD incidence (6). For many years, however, there has been some evidence that total mortality is elevated at low TC levels (18-21) and that all-cause mortality risk may be increased by cholesterol lowering (1-7).

This article reviews evidence concerning these relations and discusses whether the observations can be attributed to confounding or are causal.

Research into low TC level and disease risk should seek to understand the observed relations of low blood cholesterol with a variety of nonatherosclerotic diseases, not just cancers. The epidemiology of blood cholesterol needs to be extended to epidemiologic studies of level and function of cholesterol elsewhere in the body. The connection of laboratory and clinical studies of the cell biology of cholesterol to specific pathogenesis is often weak.

FINDINGS LEADING TO A 1990 CONFERENCE

The National Heart Lung and Blood Institute (NHLBI) sponsored the *Conference on Low Cholesterol: Disease Associations*, held in Bethesda in October 1990 (18). Before this conference, there had been three major examinations of the U-shaped risk curve of TC with total mortality (19–22); the results were synthesized from many cohort studies of TC and cardiovascular disease. Researchers had few biologic hypotheses relating low TC to any disease, as persons with low TC levels appear generally healthy (23) and were known to suffer little from atherosclerotic diseases, a major scourge of affluent society. They reasoned that any biological relations of TC to disease would be as specific as the known relation of TC to atherosclerosis. The most likely set of diseases related to low TC levels was considered to be cancer, a notion bolstered by biologically based ideas concerning colon cancer risk and TC. Cancers are the second leading cause of death in the United States, after CHD. Given that heart disease risk is positively related to TC level, and that total mortality risk is flat or inversely related to TC, it seemed logical that cancer would be inversely related to TC.

A 1981 NHLBI conference on cholesterol and cancer found inconsistent evidence that low TC is associated with increased cancer mortality (19, 20). The report stated: “While there is inconsistent but concerning evidence of a possible increase in cancer risk at very low cholesterol levels (below 180 mg/dl) in men, the magnitude of this risk is generally modest when present. Physicians can feel confident in advising reduction of blood cholesterol levels for all persons with higher than average levels” (19). The conference concluded that the findings represented a scientific, but not a public health, challenge and that the data did not preclude, countermand, or contradict the current public health message for those with elevated TC levels to reduce them through diets lower in saturated fat and cholesterol.

The International Collaborative Group study on TC and cancer (21) pooled cancer mortality data in 61,567 men from ten Western studies and ten years of follow-up, plus a Japanese study with five years of follow-up. Blood TC levels were about 30 mg/dl lower in men dying within one year of baseline of lung, colon, or any other cancers than in survivors. In subsequent follow-up years (except years 6 and 9), blood cholesterol levels were slightly lower in

cancer decedents than in survivors. Compared with survivors, a consistently lower TC was seen in lung cancer, but not in colon cancer, decedents in follow-up years 2 through 10. Based on the reduction in mean cholesterol difference between decedents and survivors in years 2 through 10 of follow-up, compared with the first year of follow-up, and the smallness of this difference in years 2–10, the authors concluded that the overall and site-specific findings on cancer death were consistent with the hypothesis that an inverse association between TC and cancer was a reflection of the effect of disease on TC level, and did not substantiate a hypothesis that low TC increases risk of cancer.

Law & Thompson (22) extended the analyses of the International Collaborative Group to a synthesis of cancer case-noncase differences in TC in 22 mortality and 11 incidence studies. They studied cancer at all sites combined, as well as lung, colon, and hematopoietic cancers. Their results closely resembled those of the International Collaborative Group (21): considerably lower TC levels in fatal cases that occurred within five years of blood measurements, or in incident cases within two years of blood measurements, than in survivors. Much smaller, but still statistically significant, differences, on the order of 1–2 mg/dl, were seen in cases occurring later. Law & Thompson interpreted these case-noncase differences for all cancers as corresponding to about a 15% greater incidence in the lowest TC quintile. No evidence of a TC difference was found for late cases of colon cancer, but differences were reported in late cases of lung and hematopoietic cancers. The authors noted that the absolute risk for cancer at low TC, even if causal, is small. They speculated on possible confounding caused by socioeconomic status, smoking, and utilization of cholesterol by growing tumors (22).

The most recent synthesis of cohort studies was motivated by observations in the Multiple Risk Factor Intervention Trial (MRFIT) Screening Follow-up Study concerning epidemiologic correlates of hemorrhagic stroke. The study of hemorrhagic stroke in the MRFIT Screening Follow-up Study was motivated by Japanese epidemiologic (24–30), clinical, laboratory, and pathologic studies (31–34), which suggested that the incidence of intracranial hemorrhage was greater among those who had low levels of TC. The Japanese investigators concluded that low TC level caused arteriolosclerosis and angioneclerosis resulting in this type of stroke. Most Western investigators interpreted that the relationship between low TC and hemorrhagic stroke was confounded by some aspect of Japanese life, for instance high salt, low animal protein, or high alcohol intake, coupled with endemic hypertension. If so, an epidemiologic study of Westerners, with lower salt, more animal protein, and lower alcohol intake, coupled with lower blood pressure levels, should find no relationship between low TC and hemorrhagic stroke.

The MRFIT Screening Follow-up Study (not to be confused with the randomized MRFIT study of the effects of multifactor intervention on CHD) of

fatal stroke was a cohort design in a convenience sample of 361,662 men. The men were initially aged 35–57 years, with TC, blood pressure, smoking, age, history of prior myocardial infarction, and history of diabetes measured or queried at baseline; they were followed for 11–13 years by death certificate linkage (35). Low TC level, defined as <160 mg/dl, was found in about 5% of the population; thus because of the large size of the MRFIT study, the sample included 21,185 men with low TC levels among the 350,977 men with no history of myocardial infarction or diabetes.

In summary, there were 83 hemorrhagic stroke deaths in six years of follow-up, for which hypertension was the predominant risk factor, explaining 32% of the attributable risk. However, 11 of these deaths occurred in men with TC <160 mg/dl, when only three to four were expected, thus constituting a relative risk of 3. Longer follow-up showed a relative risk of 2 (36), with higher mortality rates of hemorrhagic stroke for TC <160 mg/dl, regardless of blood pressure level. The 55 cases of subarachnoid hemorrhage (occurring in larger arteries and at a younger age) showed no relation to TC. The 92 deaths attributed to thromboembolic stroke, or to stroke of uncertain origin, were positively related to TC level.

The 83 deaths attributed to hemorrhagic stroke constituted only a small fraction of the 6902 total deaths in six years of MRFIT follow-up. The finding of elevated risk associated with low TC in this rare condition was considered of little public health importance for the United States. Nevertheless, to put this small excess mortality risk associated with low TC into a public health perspective, the investigators examined the risk of all cause death according to TC level. There was a consistently greater total cardiovascular and coronary heart disease death rate with higher TC levels, except at the very lowest levels of TC. However, the greater risk with greater TC was not the rule in noncardiovascular diseases. In this case, risk was greater at lower levels of TC. Combined cancer and other noncardiovascular diseases comprised more than half of total deaths.

The investigators examined the data by cause of death for total cancer, respiratory disease, trauma, and all other causes combined in unpublished analyses designed to understand these observations better. Mortality due to each of these noncardiovascular causes was greater at low TC levels, even after omission of deaths in the first three years after baseline. The overall result of these opposing epidemiologic findings was a U-shaped curve of TC level with total mortality: higher at the extremes and lower at intermediate values, i.e. 160–219 mg/dl (4.14–5.66 mmol/L).

The MRFIT study on hemorrhagic stroke and low TC (35) concluded that the increased total mortality in the lowest cholesterol-level group of men resulted mainly from an increased risk of death from diseases, particularly cancers, which have the potential to lower serum cholesterol level (37, 38).

However, the need to understand these and other findings led to the NHLBI-sponsored conference in October 1990.

THE OCTOBER 1990 CONFERENCE ON LOW CHOLESTEROL: DISEASE ASSOCIATIONS

A meta-analysis of mortality findings in relation to baseline TC in cohort studies was carried out at the 1990 conference (18). Participants in the meta-analysis were responsible for 19 studies (the MRFIT Screening Follow-up Study and ten others from the United States, one from southern Europe, one from Israel, two from Great Britain, one from Scandinavia, and three from Japan) of 20 invited to participate in the conference. The analyses were done separately for 350,977 men from the MRFIT Screenee Study (21,499 deaths), 172,760 men from other studies (34,026 deaths), and 124,814 women (12,881 deaths in 12 studies), aged 35–69 and free of CHD at baseline. Approximately 45% of deaths were coded to total cardiovascular causes, 33% to total cancer causes, and 22% to noncardiovascular, noncancer causes. The latter category included respiratory, digestive, traumatic, and other causes, comprising 5%, 4%, 6%, and 7% of total mortality, respectively. Length of follow-up ranged from 9 to 30 years. To attempt to account for the potential effects of preexisting illness on the entry TC level and subsequent disease relationships, data on deaths occurring within five years of baseline were excluded. Proportional hazards regressions for mortality on TC level were pooled (39) after adjustment for age, diastolic blood pressure, cigarette smoking, body mass index, and alcohol intake, where available (alcohol intake was available in only 12 studies).

In the meta-analysis (18), risk for 6% of men with TC <160 mg/dl or 30% of the men with TC \geq 240 mg/dl was elevated by about 15% compared with men with TC levels either 160–199 mg/dl or 200–239 mg/dl. For women, the risk curve of all cause mortality was nearly flat across TC levels. There was a graded, increasing risk for CHD death. Relative risks for CHD mortality were 2.2 among MRFIT Screenees, 1.7 among pooled men, and 1.6 among pooled women, comparing those with TC \geq 240 mg/dl with those with TC in the reference class of 160–199 mg/dl. Intermediate relative risks of 1.5, 1.2, and 1.1, respectively, were reported for those with TC 200–239 mg/dl. In contrast, total cardiovascular disease deaths were higher according to TC in men, but not in women. Relative risks for total cardiovascular disease death in those with TC \geq 240 mg/dl compared with those in the reference class were 1.9 among MRFIT men, 1.5 among pooled men, but only 1.1 among pooled women. The increased risk for total mortality at lower levels of TC resulted largely from an inverse relation with deaths due to respiratory disease, digestive disease, trauma, and residual deaths in both sexes, and to some

cancers in men only (e.g. lung, but not colon). Lesser risk with greater TC was graded for deaths due to lung cancer, respiratory disease, and digestive disease. Greater risk for trauma and residual deaths was seen only for TC <160 mg/dl. Compared with those with TC level 160–199 mg/dl, risk for combined noncardiovascular, noncancer causes of death was 45% higher for men and women whose level was low, <160 mg/dl, and 15% lower in both sexes for those whose level was high, ≥ 240 mg/dl. Parallel analyses showed that these risk patterns for all-causes, cardiovascular, cancer, and other deaths were similar within smoking and alcohol strata.

Detailed analyses from the MRFIT Screening Followup Study (36) indicated that increased death rates for those men who entered with low TC level occurred especially for hemorrhagic stroke; cancers of the lung, liver, lymphatic system, and hematopoietic systems; chronic obstructive pulmonary disease; cirrhosis of the liver; and suicide. The increased risk at low TC for lung cancer and for chronic obstructive pulmonary disease was far greater in smokers than in nonsmokers, as was also the case in the Whitehall study (40). Other causes of death were less frequent or had less strong associations with low TC levels, for example, stomach and some other digestive and nervous system cancers, other respiratory diseases, and other liver and digestive diseases; alcohol dependence syndrome; and noncancerous diseases of the central nervous system. After all these diseases had been accounted for, all remaining noncardiovascular, noncancer causes of death had excess risk at low levels of TC. Most of these findings held when data on the first five or ten years of deaths after baseline were removed from the analysis. The Honolulu Heart Program (41) was much smaller, and therefore had less power for detailed examination of the data than the MRFIT study. However, the Honolulu Heart Program found excess risk for hemorrhagic stroke (41, 42). Mortality risk at low TC levels persisted for all cancer, chronic obstructive pulmonary disease, benign liver disease, and unknown causes (41), even removing the first ten years of deaths.

RESULTS OF CLINICAL TRIALS

The meta-analysis of clinical trials by Holme (1) considered 19 multi- or single-factor, drug or diet, primary or secondary trials of TC lowering. They showed a clear reduction of CHD occurrence. The greater the net reduction in TC, the greater was the reduction in total mortality. There was, however, greater total mortality with greater reduction of TC in primary prevention trials ($p = 0.05$); there was a similar tendency in single factor studies.

Holme's (1) meta-analysis of secondary prevention trials was in agreement with that of Rossouw et al (43), which, among eight clinical trials of TC lowering, found an odds ratio of 0.78 for treated to control patients for

recurrent myocardial infarction ($p < 0.0001$). The odds ratio was 0.88 for cardiovascular deaths ($p = 0.05$), which comprised 82% of all deaths in these studies. Cancer mortality was reduced in the treated groups (odds ratio 0.75, $p = 0.26$). However, no difference was found between treated and control subjects in noncardiovascular, noncancer deaths (44). Not considered was a single secondary prevention trial of TC lowering by partial ileal bypass surgery. This trial found no excess noncardiovascular deaths in the treated group (9).

As Holme (1) noted, three multifactor primary prevention trials found no excess noncardiovascular death among treated subjects (10–13); a recently reported fourth trial showed an excess of cardiac and violent deaths in treated subjects (14). There was extensive use of drugs to lower blood pressure and TC in this latter study.

The meta-analysis by Muldoon et al (3) of six randomized, primary prevention, drug, or diet clinical trials of TC lowering found decreased mortality from CHD in the treated compared with control groups. The meta-analysis showed greater violent and cancer deaths, but not remaining causes of death, in treated versus control groups. They attributed observed increases in cancer deaths to specific effects of clofibrate in the World Health Organization study of this drug (7). Davey Smith & Pekkanen (2) studied primary prevention studies only. They added to Holme's list a nonrandomized diet study, a short follow-up of a trial using lovastatin (45), and extended follow-up from the Helsinki Heart Study (46). They analyzed diet versus drug studies separately. Mortality from CHD was reduced in treated groups in both diet and drug studies. Mortality from cancer, injury, and other noncoronary heart disease causes was greater in treated subjects of drug studies, but differences in rates were small and not statistically significant in diet studies.

Taken as a whole, the evidence for excess noncardiovascular mortality in clinical trials of TC lowering appears in primary prevention studies, in which risk of noncardiovascular disease is relatively greater than in secondary prevention studies. Adverse effects of drugs might also be suspected as a cause of the excess. In principle, interpretation of the noncardiovascular endpoints of randomized clinical trials should use the same rules of inference as interpretation of cardiovascular endpoints; therefore, the greater rates of noncardiovascular death in treated subjects should not be attributable to confounding. The clinical trial evidence should be treated with caution, however, as power is low for study of noncardiovascular disease in these trials; although the evidence is consistent, the level of statistical significance remains marginal in many analyses of studies to date. Only mortality is monitored, and rates are too low for inferences to be made about individual diseases. Several different drugs have been studied; it may be inappropriate

to pool drug studies, because different drugs have different actions and side effects. Power is low for combined noncardiovascular causes in diet trials, which comprise many fewer person-years of follow-up than do drug studies.

COULD THERE BE A COMMON BIOLOGICAL BASIS FOR THE OBSERVATIONS IN COHORT STUDIES AND CLINICAL TRIALS?

Low TC measured in cohort studies reflects a history of low TC. This is physiologically different from the relatively brief period of TC lowering in persons with elevated TC in clinical trials. Long-term low TC might have a relatively small effect on each organ system; only after many years, perhaps in conjunction with another disease process, a relative deficiency of cholesterol in cells and tissues may cause a clinical problem. Recently lowered TC in clinical trials might selectively lower cell cholesterol in certain organs, even while TC remains relatively high. Clinical manifestations would depend on which organs were most affected by the particular method of TC lowering.

POTENTIAL SOURCES OF CONFOUNDING AS A BASIS FOR THE OBSERVED RELATIONSHIPS

Although the finding of excess hemorrhagic stroke and excess mortality from noncardiovascular disease in cohort studies is strong and consistent, it may nevertheless be a reflection of epidemiologic confounding. The cohort studies were designed to measure possible confounders for cardiovascular disease, but paid little attention to noncardiovascular diseases and their causes. Several possible confounders have been suggested.

The first confounder is that disease lowers TC levels, so that the excess risk is simply due to a disease that the person already had when TC was measured. Total cholesterol will be lowered by virtually any disease in its final, wasting phases. The first five to ten years of deaths were excluded from analysis in the 1990 NHLBI Conference (18) and related papers (36, 41), in an attempt to eliminate those who might have had unnoticed disease at baseline. This strategy for avoiding confounding appears to be adequate with respect to cancer, which may lower TC four years (47) and possibly as long as ten years, before death (48). However, latent or undetected disease at baseline is a real possibility in these studies; for example, nonlife-threatening liver disease, cholesterol malabsorption, or reduced lung function was not even noted in most cohort studies of the development of CHD. One may survive for many years with a cirrhotic liver, intestinal disease, or reduced lung function. Little is known about when and by how much TC might first be reduced in the course of such diseases.

Any disease risk factor that lowers TC, including cigarette smoking or alcohol intake, can be a confounder. Excessive alcohol intake may lead to malnutrition and/or a compromised liver, either of which might lower TC and cause death by mechanisms independent of TC level. Or, TC may play a role only in certain conditions; for example, low TC may be important in lung disease only among smokers (36, 40). Total cholesterol may affect noncardiovascular disease indirectly, only when a risk factor is present. For example, smoking lowers serum high-density lipoprotein (HDL) cholesterol, which might affect noncardiovascular diseases through its role in steroid hormone production by the ovaries and the adrenal gland (49) and pulmonary surfactant production (50–52).

Dietary factors might lower cholesterol incidentally, while causing disease by mechanisms independent of TC level. For example, vitamin E might influence noncardiovascular disease by affecting cell membrane characteristics. Vitamin E-deficient rat lung microsomes and lipid vesicles (compared with vitamin E sufficient ones) had more cholesterol, more readily oxidized lipids, and decreased fluidity (53). In another example, diets high in vitamin E tend to be high in fruits, vegetables, legumes, and whole grains and are, therefore, likely to result in relatively lower levels of LDL cholesterol. Yet, because LDL lipoprotein is the primary carrier of vitamins E and β -carotene, the resulting low levels of serum LDL cholesterol may carry inadequate amounts of fat soluble antioxidant vitamins E and β -carotene to tissues. Relative antioxidant deficiency may occur when their transport capacity is reduced. That such reduction may have clinical importance is suggested by inhibition of function of fat-soluble drugs, such as cyclosporine, when LDL is low (54).

Low socioeconomic status may be a confounding factor in the low blood cholesterol:disease relationships (22, 40). Many characteristics of poverty, such as infection or violence, predispose to disease. Poverty may also be associated with poor diet quality or alcoholism, both of which may lead to low TC, independent of any effects TC might have on disease risk.

POTENTIAL BIOLOGIC BASES FOR THE OBSERVED RELATIONSHIPS

One may hypothesize that either an excess or a deficiency in functions related to cholesterol metabolism could lead to excess disease risk. There is wide evidence that cholesterol is essential to, and intimately involved with, many aspects of cellular structure and function (55, 56). For example, cholesterol affects the fluidity of cell membranes, membrane permeability, transmembrane exchange, signal transmission, and other cell properties. Cholesterol is a precursor for five major classes of steroid hormones. It affects gluconeo-

genesis and immune function; its transport forms, the lipoproteins, also serve as vehicles for fat-soluble vitamins, antioxidants, drugs, and toxins. Thus, cholesterol plays general, fundamental, and highly specific roles in the economy of the body.

Cell membrane abnormalities, such as increased or decreased fluidity, are found in many diseases, including atherosclerosis [aortic cell membranes in rabbits (57) and erythrocytes in humans (58)], Type I diabetes [erythrocytes in humans (59)], infection [erythrocytes in sheep (60)], obesity [erythrocytes in children (61)], Crohn's disease [erythrocytes in humans (62)], spinocerebellar degeneration [erythrocytes in humans (63)], chronic liver disease and nephrotic syndrome [erythrocytes in humans (58), and rats (64)], hypothyroidism [erythrocyte and brain subcellular fractions in rats (65)], maternal alcohol use [brain sections in rat pups (66)], and Alzheimer's disease and vascular dementia [white matter in autopsies (67)]. We do not know the causes of these cell membrane abnormalities. Nor do we know whether the abnormalities are in any way related to level of cholesterol in the blood.

Changes in cell membrane cholesterol levels may result in changes in other functional characteristics of the cell membrane. For example, fluidity in porcine pulmonary artery endothelial cells decreased when incubated in cholesterol and transmembrane serotonin transport correspondingly decreased (68). Engelberg (69) speculated that low levels of cerebral serotonin, secondary to low serum cholesterol, may reduce impulse control, thereby increasing likelihood of suicide or aggressive behavior. Some immune functions depend on membrane cholesterol. Roosemond et al (70) studied the effect of altered target cell membrane structure on natural killer (NK) cell-mediated cytotoxicity. Both human and rat NK-resistant cell lines became NK-sensitive (that is, were lysed by NK cells) after fusion with NK-sensitive membrane components. The fusion required the presence of Sendai virus envelope glycoproteins, soybean lecithin, and cholesterol for maximum efficiency. Heiniger et al (71) found that cytolytic function of mice T lymphocytes was strongly suppressed in a medium with an inhibitor of cellular cholesterol synthesis (25-OH-cholesterol). The effect was reversed when cholesterol or mevalonic acid was added to the culture medium. Because similar inhibition of DNA synthesis had no effect on cytolytic activity, the authors concluded that the effect results from inhibition on sterol synthesis, rather than on inhibition of cellular proliferation.

The above authors did not study whether any of these cell membrane abnormalities is related to level or changes in TC. Mistry et al (72) showed that 750 or 1500 mg per day of supplemental dietary cholesterol resulted in higher blood TC and higher levels of cholesterol in leukocytes, but the authors did not specifically study free cholesterol, the form that exists in cell membranes. Shanmugasundaram et al (73) studied 20% [polyunsaturated fatty

acid:saturated fatty acid (P:S) ratio 0.6] and 35% fat diets (P:S ratio 0.2) and found that TC was increased on the higher fat diet. The cholesterol was increased in erythrocyte membranes and in whole leucocytes on the higher fat diet; free cholesterol in leucocytes was not studied. Andersen & Dietschy (49) showed that cholesterol in the serum is important in the regulation of cell cholesterol. However, cell cholesterol and cell function may vary at different TC levels, despite the compensatory changes that occur in cell cholesterol synthesis when TC changes. Andersen & Dietschy did not actually show that cell cholesterol level did not change. Phillips et al (74) indicated that the direction of any net transfer of cholesterol between cells and lipoproteins is determined by the molar ratios of free cholesterol/phospholipid of the donor and acceptor particles; cholesterol diffuses down its gradient of chemical potential generally partitioning to the phospholipid-rich particles, independent of any receptor processes. Gotto et al (75) stated that the distribution of LDL to various tissues depends on the rate of transcapillary transport, as well as on the activity of LDL receptors; for example, LDL uptake by the adrenal gland is facilitated by a fenestrated epithelium and cortical cells rich in LDL receptors, whereas adipose tissue and muscle have nonfenestrated capillaries and few LDL receptors and take up LDL slowly. Grundy (76) concluded that one third of cholesterol exchange between cells and serum occurs via nonreceptor mediated pathways; the amount of cholesterol incorporated into the cell via this mechanism may be more susceptible to variation with TC level than the corresponding amount via receptor-mediated pathways.

The level of cholesterol in the cell may be adequate for viability of the cell, yet be inadequate for cell products. Hass & Longmore (50) studied pulmonary surfactant and found that only about 1% of its cholesterol was supplied by synthesis in the Type II pneumocytes that produce lung surfactant. The rest of the cholesterol was supplied by the plasma; receptors for both LDL and HDL cholesterol were found (51). A recent experiment found that both HDL and LDL stimulate pulmonary surfactant secretion (52). Thus, if serum cholesterol were low, surfactant function could possibly be impaired; however, this has not been studied. Longmore and coworkers have found that surfactant chemical composition is altered in acute respiratory distress syndrome (77) and that replacement of surfactant corrects abnormalities caused in rats by experimentally injuring lungs (78). Possible alterations in the biochemical composition of pulmonary surfactant might have relevance to the consistent finding of a graded negative relationship between TC and either lung cancer or chronic obstructive pulmonary disease mortality.

Genetic errors result in low TC. In the classic, extreme example of a low TC:disease association found in the exceedingly rare individuals having homozygous abeta-lipoproteinemia, there are low circulating levels of TC

(less than 50 mg/dl) and low-to-absent circulating LDL or apoprotein-B (79). Homozygotes suffer numerous defects, including intestinal malabsorption of fat, progressive degeneration of the central nervous system, retinal pigmentary degeneration, abnormal red blood cells, and cardiomyopathy (79). The underlying biochemical defect probably involves an abnormality in the synthesis or secretion of apoprotein B-containing lipoproteins and results in a functional disturbance of delivery of cholesterol to peripheral tissues (79). Affected persons experience serious disease consequences involving multiple organ systems; however, these consequences are partly correctable by administration of large doses of vitamin E and water-soluble vitamin A and vitamin K (79). These clinical manifestations are most likely due to deficiencies in fat soluble vitamins and/or other lipid soluble factors in the blood, not just to the low LDL level. Granot & Deckelbaum (80) reported that heterozygotes who also have low TC levels, sometimes well below 100 mg/dl, nevertheless appear healthy and may be long-lived. However, Andersen et al (81) found mild impairment of function of long motor and sensory tracks in heterozygotes, which might, with long exposure, predispose to accident.

Another genetic error of metabolism related to cholesterol synthesis in the cell is mevalonic aciduria secondary to mevalonate kinase deficiency. This condition has been identified in ten children (82, 83). The defect is partially countered by increased activities of HMG CoA reductase and of the LDL receptor pathway. Total cholesterol is normal or slightly reduced. There are severe consequences: psychomotor retardation (10/10), hypotonia/myopathy (9/9), ataxia (5/9), failure to thrive (9/10), recurrent crises with fever/diarrhea (8/9), anemia (7/9), hepatosplenomegaly (5/10), cerebellar atrophy (5/7), dysmorphic features (5/10), cataracts (3/10), elevated serum creatine kinase (6/9), decreased tissue and plasma ubiquinone 10 (4/6), and death (4/10). Low doses of lovastatin in two patients worsened their conditions; plasma creatine kinase and ubiquinone worsened. These conditions are similar to those seen in dogs treated with high doses of lovastatin (84–86). Lovastatin in doses used clinically reduces mevalonic acid excretion by the kidney only by one-third (87). Because two patients treated with high doses of vitamin E, vitamin C, and ubiquinone 10 showed some improvement, Hoffmann (83) suggests that the severe multisystem pathology in mevalonic aciduria might be attributed to free radical pathology. However, the extent to which cholesterol in cell membranes or in other functions is involved in either short- or long-term prognosis of these patients is unknown.

Considerable work has been done on the biologic role of low TC in hemorrhagic stroke patients. The inverse relationship between TC level and the risk of hemorrhagic stroke suggests that hypertensive, hypocholesterolemic individuals are more liable to develop this complication than those with either

hypertension or low TC level alone (35, 36, 42). Cerebral hemorrhage occurs mostly from penetrating vessels in the basal ganglia of the brain, the intraparenchymal small arterioles of 100–300 microns in diameter. Angioneurosis, the basic pathologic finding, is not a proliferative disorder of the intima like atherosclerosis, but rather involves the disappearance of medial smooth muscle cells. Because these cells are an important component of vascular structure, their loss is thought to lead to vessel wall fragility, hypothesized to be caused by increased permeability of endothelial membranes. Vessel wall fragility, in turn, leads to the formation of microaneurysms. When microaneurysms burst, bleeding occurs. When thrombi are formed and organize in microaneurysms, lacunar infarction occurs. The presence or absence of dietary factors that exert deleterious or protective effects on endothelial and medial elements of the vessels is seen as important. Although it has not been demonstrated whether cholesterol content of endothelial cell membranes is low in humans having a low TC level, men with a history of intracerebral hemorrhage have lower cholesterol content in both serum and erythrocytes than men with no history of stroke (31). Dietary changes have been shown to relate to cell cholesterol content (72, 73). Low TC also may lead to decreased numbers of medial smooth muscle cells, a process accelerated by high blood pressure. Experimental increase of TC level in hypertensive rats from a very low level (mean 114 mg/dl) to a moderately high level (mean 242 mg/dl) was associated with attenuation of the loss of medial smooth muscle cells (32) and risk of development of stroke (33). Some other researchers have shown relationships of low TC to cell membrane function (34, 88, 89) but others have not (90). Brown et al (91) and Goldstein & Brown (92) have emphasized the powerful homeostatic mechanisms controlling cellular content of free cholesterol.

The manifold functions of cholesterol present a fundamental problem in understanding any biologic role of low TC in nonatherosclerotic disease: There are so many places to look for abnormality, yet all critical body functions of cholesterol are homeostatically well controlled. Is homeostasis adequate in all tissues in all people at all ages, even when compromised over many years by the physiologically “degrading” effects that might result from exposure to smoking, infectious agents, alcohol-induced damage, or a variety of drugs? There is a lack of fundamental information about how cholesterol in the plasma affects each of these functions, such as the role of TC level in regulation of cell membrane cholesterol, in transport of antioxidants, or in maintenance of lung surfactant. Each of these roles may be complex and may express problems in an interacting variety of ways, not only by the most obvious routes of reduced cholesterol in the membrane at low serum cholesterol levels, or modified fluidity at low TC levels.

The basis for observed relationships of low TC, or TC lowering, and disease

does not appear to be readily at hand. The excess noncardiovascular mortality in TC lowering trials, particularly those using drugs, may be related to blood and cell cholesterol in complex ways. Similarly complex may be the explanation of the excess noncardiovascular mortality at low TC levels in cohort studies. There may, in fact, be no biological connection of these diseases to TC. Confounding may be subtle. The salient epidemiologic needs for understanding this issue are to study TC in relation to morbidity, including the time course of TC change before, during, and after disease onset. The development of epidemiologic information about the relation to disease of cell and tissue cholesterol and its function should be a priority. At the same time, there is enough tantalizing biologic information available to justify vigorous study of the influence of TC on cell and tissue cholesterol and on cholesterol related function.

IMPLICATIONS FOR PUBLIC HEALTH POLICY

Several authors have recently suggested caution in the pursuit of low TC. Frank et al (41) recommended against TC lowering in persons with TC ≤ 225 mg/dl, based on models that imply that the 60% of persons in the Honolulu Heart Program with this level of TC might be harmed by TC lowering. Hulley et al (93), commenting on the 1990 Bethesda conference (18), suggested limiting TC screening and intervention to the minority for which benefits clearly predominate over harms, that is, those with coronary disease or other reasons for being at a comparable very high risk of CHD death. This recommendation was based on an association between low TC and non-cardiovascular disease death rates in men and women, the absence of association between high TC and cardiovascular disease death rates in women, and the absence of change in total mortality in primary prevention trials. Kronmal et al (94) recommended caution in initiating any TC lowering treatment in men and women above 65–70 years of age, based on inverse relationships of TC to all-cause and CHD mortality in Framingham data and the absence of clinical trials of TC lowering in the elderly. Hazzard (95) felt that it is an open question whether to treat high TC in the elderly, based on several factors, including the absence of demonstrated efficacy of TC lowering in increasing longevity. Davey Smith & Pekkanen (2) suggested a moratorium on general use of medications to lower TC in primary prevention, pending the results of ongoing trials. This conclusion was based on a meta-analysis of past trials in which drug trials had adverse effects.

The absence of a clear demonstration of efficacy of TC lowering drugs in increasing longevity makes me uncomfortable with heavy reliance on medications as a public health strategy for TC lowering (96), particularly in inadequately studied groups, such as women and the elderly. What, then, of population-wide efforts to lower TC by dietary change? Total cholesterol

changes in whole populations tend to be greater at high than at low TC levels (25, 96). Less TC lowering at low TC levels would dampen any adverse effects that might result from TC lowering (96). Although many biologic possibilities are outlined in this review, there is no definite evidence of biologically based adverse consequences, and it appears unlikely that 100% of the observed associations between low TC and nonatherosclerotic disease death is causally mediated by TC. In contrast, a causal relationship of TC level with atherosclerosis and CHD is established. Models for mortality, which consider these points, suggested net benefit from a 20 mg/dl average reduction of population TC by diet (96). These models pertained specifically to men aged 35–57 when TC was measured, starting at a mean TC of 215 mg/dl. The models suggested that the lower the starting average TC level the less the benefit. There is less information on mortality risk in women and the elderly. The Bethesda conference finding (18) of no association between TC and total cardiovascular disease death in women is provocative; in addition, premenopausal women have lower average TC than men.

Nevertheless, I consider current public health recommendations concerning eating patterns sound. Irrespective of effects on TC itself, there are many positive aspects for both men and women in the widely recommended healthy eating patterns for individuals, families, and whole populations. Prevention of CHD in high TC cultures remains a pressing need, and TC lowering has been shown to contribute to prevention. Furthermore, population-wide efforts (i.e. food industry changes, government policy, medical practice) to reduce saturated fat and cholesterol intake are important to any effective program of TC lowering; they also tend to agree with other dietary policies aimed at increasing fruit, vegetable, legume, whole grain, and fish intake (97, 98). Although current population-wide efforts to lower TC by diet should continue, there is minimal absolute benefit for CHD prevention in adults with low TC, e.g. TC <180 mg/dl, who are free of heart disease, and there is potential risk for adults with low TC. A low-risk strategy, in which population-wide policy initiatives continue, is therefore suggested, but those individuals identified with low TC and who are free of heart disease are not advised to take personal steps toward TC lowering. Almost half of the total population of the United States, namely adults with higher TC (perhaps ≥ 200 mg/dl) and those who have heart disease, would continue to be advised to pursue personal TC lowering strategies.

ACKNOWLEDGMENT

This work was done with the support and assistance of two individuals. The author thanks Henry Blackburn for leadership, friendship, and scientific acumen. John Belcher has been generous with his time and knowledge of biochemistry. The syntheses and conclusions of this review are the author's, however.

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